## REMARKS

As in initial matter, Applicants thank the Examiner for the courtesy extended during the telephonic discussion of January 8, 2004. Applicants thank the Examiner for the opportunity to discuss the application.

Upon entry of the amendments, claims 1, 3-19, 21 and 39-55 will be pending in the application. Claims1, 3-5, 7, 9-11, 16, 18, and 19 have been amended. New claims 39-55 generally correspond to claims 22-38, which are now cancelled. Support for the amendment to claim 1 appears in the specification at, e.g., original claim 1 and page 8, lines 9-10 and the paragraph bridging pages 1 and 2 of the specification (disclosing "polynucleotide molecule"); page 4, lines 5-6 (disclosing targeting elements binding within 100 nucleotides of a distinguishing element) and page 9, lines 9-15, and page 14, lines 14-16 (disclosing attachment of a separation group only if a targeting element has bound to a target sequence). Claims 3-5, 7, 9-11, 16, 18, and 19 are amended to more particularly point the claimed invention.

Support for new claim 39 appears in previous claims 1, 4-7 (disclosing that the targeting element is an oligonucleotide and the separation group is an immobilizable nucleotide). New claims 40-42 are supported in the specification at, e.g., page 4, lines 12-17. New claim 43 is supported at, e.g., previous claim 1 and page 4, lines 7-8 (disclosing covalent attachment of a separation group). Support for new claims 44-46 is found in the specification at, e.g., page 2, lines 25-26, page 4, lines 7,8,15-17, page 10, lines 26-28, and original claim 9. New claim 47 is supported in the specification by original claims 5, 7 and at page 4, lines 7-8. New claims 48 and 49 are supported in the specification at pages, 3, lines 10. New claim 48 is supported in the specification at, e.g., page 13, line 31 to page 14, line 4. New claim 50 is supported in the

specification at, e.g., page 13, line 31 to page 14, line 11. New claims 51-52 and 55 are supported by original claims 5 and at page 13, line 31 to page 14, line 4. No new matter is added by these amendments.

New claims 39-42 correspond to claim 1 as amended and further require that the targeting element is an oligonucleotide and that the separation group is an immobilizable nucleotide. New claims 43-46 correspond to previous claim 21 but require that the separation group is covalently attached to the targeting element. New claims 47-49 also require that the separation group is covalently attached to the targeting element and further require that the targeting element is an oligonucleotide and that the separation group is an immobilizable nucleotide.

New claims 50-53 correspond generally to previous claim 1 but require that the targeting element is pre-attached to the separation group, and that the binding of the targeting element-separation group to the target nucleic acid sequence is selectively stabilized in the distinction step.

**Rejections under 35 USC § 102**

Claims 1, 3-6, 10, 13-16, 18, and 21 are rejected as anticipated under 35 USC § 102(b) by Whitcombe et al., WO97/42345 ("Whitcombe"). The rejection is traversed as applied to these claims as amended and is also addressed with respect to new claims 22-38.

Applicants note the Examiner's statement in the May 6, 2003 Advisory Action that "the claims are not limited to separating and detecting a nucleic acid present in the starting population".

Applicants believe the present amendment to independent claim 1, from which the remaining claims subject to the rejection depend, addresses the Examiner's concerns. The

method specified in claim1 as amended, from which the remaining claims subject to the rejection depend, has been amended to more clearly specify that the polynucleotide removed in the final recited step (now labeled step (e)) is the same polynucleotide molecule specified in step (a) of the recited method. That is, the removed polynucleotide is present throughout the recited steps, from step (a) through the subsequent contacting, attaching, and immobilizing steps (steps (b)-(d)).

In contrast, the method described in Whitcombe does not result in the isolation and detection of the actual polynucleotide molecule itself from a starting population of nucleic acid molecules. Instead, Whitcombe describes a method in which a series of extension products are prepared. The first extension product is generated from a diagnostic primer that includes a tail sequence with a tag region and a detector region (see page 1, line 28-page 2, line 4). The extension product then acts as a template for the extension of a further primer that hybridizes to a locus at a distance from the diagnostic base sequence; the further primer when extended forms a further extension product (page 2, lines 5-10; see also claim 1). The presence or absence of a diagnostic base sequence is detected by reference to a detector region in the further extension product using methods discussed at page 2, line 11, to page 3, line 6 and claims 2-6.

Thus, Whitcombe describes a method that detects not the starting polynucleotide molecule itself but instead an amplification product whose synthesis is dependent on the presence of a particular polynucleotide molecule. For this reason, this reference does not describe the invention of claim 1 and its dependent claims, claims 3-6, 10, 13-16, 18, and 21.

New claim 39 corresponds to the subject matter of previous claim 21, along with previous claims 4-7. Claim 7 is not subject to the rejection for anticipation by Whitcombe.

Therefore, new claim 39, along with its dependent claims 40-42, and new claims 47-49, are not described by this reference.

New claims 43-46 require that the separation group be covalently attached to the targeting element that is bound to a target sequence in a nucleic acid molecule of interest. The requirement of covalent attachment of the separation group distinguishes the claimed invention from Whitcombe, which describes a method in which a detector species (corresponding to Applicants' separation group; see page 6, first paragraph of the December 19, 2002 Office Action) associates non-covalently with a detector region in an nucleic acid sequence element termed a "further extension product" (corresponding to Applicants' targeting element).

New claims 47-50 require that the targeting element contacts the polynucleotide molecule with the separation group already attached; and that the targeted / immobilized polynucleotide molecule is present from the outset. Whitcombe also fails to describe this feature of the claimed invention (see also page 2, lines 22 in Whitcombe, which specifically excludes "other nucleic acid sequences in the sample").

Claims 1, 3-15, 17, 18, and 21 are rejected as anticipated under 35 USC § 102 (e) by Lundeberg et al., US Patent No. 6,482,592 ("Lundeberg"). The rejection is traversed to the extent it is applied to the claims as amended.

The Examiner states in the May 6, 2003 Advisory Action that "the claims do not recite limitations wherein the attachment of the separation groups is indispensable to the presence of the bound targeting element and distinguishing element in the vicinity of the bound targeting element."

To address the Examiner's concern, all of the pending claims now specify that attachment of the separation group occurs only if the targeting element is bound to a target sequence on the polynucleotide molecule.

Lundeberg does not describe this feature of the claimed invention. The Examiner states that the modular oligonucleotide described in Lundeberg corresponds to a targeting element, and that a modulating module/capture probe corresponds to a separation group (page 8, second paragraph of the Office Action). Lundeberg teaches that binding of the modular oligonucleotide - which includes "at least two modules", or parts (column 1, line 59; and column 6, line 51) - is improved relative to a single oligonucleotide through the mutual interaction of the two adjacent modules, i.e. the further module / modulator and the capture / detection module (column 6, lines 42-45) . However, the binding of neither the "further module / modulator" ('targeting element') nor of the "capture / detection module" ('separation group') is a necessary prerequisite for binding of the other module. Each part of the modular oligonucleotide is itself a single oligonucleotide of significant length (column 1, line 64; Figs. 3A and 3B) and will bind to the target nucleic acid molecule even in the complete absence of the other, albeit at a decreased efficiency due to the absence of the effect described here. . Thus, Lundeberg does not describe a method in which attachment of the separation group ('capture / detection module') occurs only if the targeting element ('further module / modulator') is bound to a target sequence on the polynucleotide molecule in the presence of a distinguishing element in its vicinity, and so fails to anticipate the invention of claim 1 and claims depending from claim 1.

In view of the foregoing comments, Applicants respectfully request reconsideration and withdrawal of the rejections for anticipation.

**Rejections under 35 USC § 103(a)**

Claim 16 is rejected as unpatentable over Lundeberg in view of Whitcombe. The rejection is traversed.

Claim 16 depends from claim 1 and further requires that the distinguishing element is a single nucleotide polymorphism. As is explained above, Lundeberg does not make obvious the invention of claim 1 because it discloses oligonucleotides as targeting elements and separation groups. Binding of the oligonucleotides is not obligatory, but instead is, according to Lundeberg, enhanced when both oligonucleotides are present. Lundeberg neither discloses nor suggests any separation groups that bind only if the targeting element is bound to a target sequence on the polynucleotide molecule and a distinguishing element is present within 100 nucleotides of the target sequence..

Whitcombe is used to complete the rejection by teaching the identification of single nucleotide polymorphisms. However, it, fails to disclose or suggests a separation group that binds only if a distinguishing element and a bound targeting element are present within 100 nucleotides of a particular polynucleotide molecule, and wherein the polynucleotide molecule is present in a provided population of nucleic acid molecules (see first recited step), as well as during the subsequent contacting, attaching, and immobilizing steps. Thus, claim 1 is non-obvious over the combination of Lundeberg and Whitcombe. Because claim 16 depends from claim 1, it too, is non-obvious over the combination of Lundeberg and Whitcomb. Therefore, the cited references do not render claim 16 prima facie obvious.

Claim 19 has been rejected as obvious over Lundeberg. The rejection is traversed. Claim 19 is drawn to a method in which removal of the separation group occurs only if the distinguishing element within 100 nucleotides of the bound targeting element is absent. There is

no suggestion in Lundeberg of a method with this step. Therefore, claim 19 is not *prima facie* obvious over this reference, and Applicants respectfully request reconsideration and withdrawal of the rejection for obviousness.

The Commissioner is hereby authorized to charge payment of any fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 22650-001CIP).

Respectfully submitted,

Date: January 15, 2004

David E. Johnson No. 41,874
Attorney for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

TRA 1871744v2

**Certificate of Transmission under 37 CFR 1.8**

I hereby certify that this correspondence is being transmitted by facsimile to the United States Patent and Trademark Office on **January 15, 2004.**

Donna R. Doyle
Signature

Donna R. Doyle
Name of person signing the Certificate

The papers submitted with this facsimile include:

1. Transmittal Letter;
2. Supplemental Response to December 12, 2002 Office Action.

TRA 1875098v1